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ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/506,962	ULLRICH ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,8 and 10-18* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 8, 10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 8, and 10-18 are all the pending claims in this application.

2. Claim 16 was amended and new Claim 18 added in the Response of 5/6/10.

3. Claims 11 and 12 are withdrawn from examination.

4. Claims 2, 8, 10 and 13-18 are all the pending claims under examination.

5. This Office Action is final.

Withdrawal of Objections

Claim Objections

6. The objections to Claims 13 and 16 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn.

Applicants have attended to the objection by amending Claim 16 to differ from and to narrow the subject matter of Claim 13.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

7. The rejection of Claims 2, 8, 10 and 13-17 (and new Claim 18) under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained because the claims recite subject matter for an antibody a) which binds pro-HB-EGF; b) inhibits activation of any growth-factor receptor of the EGFR family much less HER-2, HER-3 or HER-4; *and* c) is therapeutically effective *in vivo* against at least one cancer including at least one of colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, and where the cancer activity is proliferation, cell migration, invasivity or anti-apoptosis.

Applicants were not in possession of an antibody having all of the claimed properties at the time of filing.

For purposes of review, the rejection was set forth in the Office Action of 7/16/08 as follows:

"Claims 2, 8, 10 and 13-17 recite subject matter for "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" that is not defined in the specification (*In re Morris* 127 F.3d 1048, 44USPQ2d 1023 (Fed. Cir. 1997) and MPEP 2163).

The specification discloses "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF." The specification does not otherwise cite a commercial example(s) of such an antibody or reduce to practice any antibody meeting all of these properties. The prior art does not support the existence of any such antibody.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001)), the claimed invention must meet the following criteria as set forth.

Actual reduction to practice: the specification does not show any embodiments that meet the limitations for "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" reduced to practice.

Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the claimed invention as a whole (i.e., using the antibody to prevent or treat cancer).

Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the antibody.

Method of making the claimed invention: the specification does not teach or suggest how to make "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF".

Level of skill and knowledge in the art: the examiner's search of commercial literature databases (Medline, CAPLUS), the ATCC website and the ExactAntigen database did not reveal the existence of any "antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF."

Predictability in the Art: one of skill in the art could reasonably expect to generate an antibody that binds the pro-HB-EGF protein but it is not predictable that the antibody would also inhibit processing of said pro-HG-EGF or that the same antibody could be administered in a subject and still exhibit the same properties.

Applicants' specification does not show the existence of a commercial antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF. Applicants' specification has not reduced to actual practice a working example of an antibody with these characteristics. One of skill in the art could reasonably conclude that

Applicants were not in possession of "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" at the time of application filing.

The rejection was maintained in the Office Action of 3/3/09 as follows:

"Applicants allegations on pp. 4-7 of the Response of 11/17/08 that the identity of the antigen is well known (e.g., the interpretations of decisions of Noelle v. Lederman; In re Bucher; Hybritech, Inc. v Monoclonal Antibodiesd, Inc.; and Capon v. Eshar; the PUBMED search output for pro-HB-EGF (Exhibit A); the GenBank accession no. for pro-HB-EGF (M60278) in WO 01/35889; methods for making antibodies (Kohler et al., (Nature, vol. 256; pp. 495-497, 1975) and Mathews and Wells (Science, vol. 260, pages: 1113-1117, 1993)); processing of nerve growth factor (Exhibit B (PUBMED search) and the review article by Seidah et al. (Biochem J., 1996)), is not considered to support an antibody which meets all of the functional limitations required of the instant method claims.

Response to Arguments

Applicants have failed to show the existence of appropriate epitopes/regions of the target entigen, pro-HB-EGF, that would provide the claimed functional properties required of the antibody. The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004). The problem here is that the instant specification fails to provide a disclosure of which antibody retain the appropriate antibody specificity for pro-HB-EGF *and* which blocks the processing of pro-HB-EGF. A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property. There is insufficient guidance and direction as to the written description of the claimed antibody, as broadly encompassed by the claimed invention. Given the well known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention; one of skill in the art would conclude that applicant was not in possession of the functional attributes of a representative number of species possessed by the members of the genera of "an antibody which binds to pro-HB-EGF and which blocks the processing of said pro-HB-EGF" as indicated above, and broadly encompassed by the claimed invention. One of skill in the art would conclude that the specification fails to disclose a representative number of species much less a single species to describe the claimed genera.

The rejection was maintained in the Office Action of 11/6/09 as follows:

"Applicants allegations on pp. 4-5 of the Response of 9/3/09 have been considered and are not found persuasive.

Applicants rely on Example 13 of the Written Description Training Materials in providing guidance on the written description of antibody molecules and manner of claiming them for satisfying the written description requirements under 35 USC §112, ¶ 1, and they excerpt the example for Claim 1. Applicants allege in view of the PTO's own written description guidelines, the specification's disclosure of a well- characterized antigen (such as, for example, pro-HB-EGF), and the manner of using such antibody molecules in immunotherapeutic applications, such was not only well-described in the medical literature but also routine for clinicians and medical professionals in the field of cancer biology. Applicants allege the molecules are now described with respect to their ability to bind to pro-HB-EGF, and conform to the written description guidelines.

Response to Arguments

Initially the examiner submits that contrary to Applicants assertion, the claims encompass functionalized antibodies wherein the antibodies are not only required to recognize and bind to the pro-HB-EGF antigen but also yield a functional result, namely, that it inhibits activation of any growth-factor receptor of the EGFR family much less HER-2, HER-3 or HER-4 and is therapeutically effective in vivo against at least one cancer including colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, *and* where the cancer activity is proliferation, cell migration, invasivity or anti-apoptosis.

Secondly, Applicants representative states on the record and urges the Office to believe that immunotherapeutics is well-described in the medical literature and routine for clinicians and medical professionals in

the field of cancer biology absent a showing of authority for this assertion. Absent a showing to the contrary, arguments of counsel alone are not found to be sufficient in overcoming the rejection (MPEP 2144.03).

Thirdly, a prong in the written description test is the predictability in the field of art for the claimed invention or elements thereof. Here Applicants have yet to site a single example of an antibody actually having been reduced to practice and for which Applicants were in possession at the time of filing. Applicants have not created an antibody meeting all of the requirements of the instant claims. Applicants have not shown the existence of an antibody produced by others or commercially available that meets all of the claimed requirements. Applicants have not disclosed a genus of antibodies meeting the structure/function correlation for the instant claimed antibodies.

Applicants allegations on pp. 5-9 of the Response of 5/6/10 have been considered and are not found persuasive.

a) Applicants allege that under *Ex parte Sorenson* 3 U.S.P.Q.2d 1462 (BPAI, 1987), it was held that the test for determining whether a claimed invention is adequately described in the specification is whether the originally filed disclosure reasonably conveys to a person having ordinary skill in the art that the applicant had possession of the subject matter later claimed; and under *In re Smythe*, 480 F.2d 1376, 1384 (C.C.P.A. 1973), the court further held that it is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art to which the invention pertains would recognize from the disclosure that the Applicant's invention included those limitations.

Response to Arguments

The examiner submits that the facts under *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) are inapposite to the instant claimed antibody. Under *Smythe* the phrase “air or other gas which is inert to the liquid” was sufficient to support a claim to “inert fluid media” because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant’s invention includes the use of “inert fluid” broadly (MPEP 2163). This is

inapposite to the instant claimed method requiring that the subject matter, rather then being inert is instead *the* critical, functional element to the method itself, namely, the functionalized antibody much less having to meet all of the structure/function requirements of the claims. MPEP 2162 states in part:

"The Federal Circuit has explained that a specification cannot always support expansive claim language and satisfy the requirements of 35 U.S.C. 112 "merely by clearly describing one embodiment of the thing claimed." *LizardTech v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346, 76 USPQ2d 1731, 1733 (Fed. Cir. 2005). The issue is whether a person skilled in the art would understand applicant to have invented, and been in possession of, the invention as broadly claimed."

The examiner submits that the facts under *Ex parte Sorenson* 3 U.S.P.Q.2d 1462 (BPAI, 1987) are inapposite to the instant claimed antibody. Under *Sorenson* the subgeneric language of "aliphatic carboxylic acid" and "aryl carboxylic acid" did not violate the written description requirement because species falling within each subgenus were disclosed as well as the generic carboxylic acid. This is inapposite to the instant claimed method requiring actual reduction to practice of *the* critical, functional element to the method itself, namely, a functionalized antibody meeting all of the structure/function requirements of the claims. The examiner has established on the record that functionalized antibodies for method treatment use are unpredictable and comparison to the facts of *Sorenson* is an irrelevant and non-analogous art.

b) Applicants allege that under MPEP 2163 all that is required to satisfy written description is that the specification teaches the steps for the claimed invention; here,

Marikovsky et el . (PNAS, 1993) shows polyclonal anti-sera against HB-EGF, a PubMed search reveals such antibodies before the priority date and antibodies fitting the description are commercially available.

Response to Arguments

The examiner resubmits that Applicants have filibustered the prosecution proceeding by presenting attorney arguments and irrelevant reference articles which do not even describe the binding property of the instant claimed antibody, namely, that it recognizes pro-HB-EGF. All of the extrinsic evidence discussed is for antibodies that bind HB-EGF. Using binding specificity as the first and foremost functional requirement of the antibody, then Applicants still have not shown that they were in possession of this kind of antibody at the time of filing. Moving on to the remaining functional requirements for the same antibody, namely, that it a) inhibits activation of any growth-factor receptor of the EGFR family much less HER-2, HER-3 or HER-4; b) is therapeutically effective *in vivo* against at least one cancer including at least one of colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, *and* c) where the cancer activity is proliferation, cell migration, invasivity or anti-apoptosis, then Applicants still have not shown that they were in possession of this antibody at the time of filing.

c) Applicants allege representative examples in the specification, further in view of the experimental evidence provided in the Huber declaration, reasonably convey to a skilled worker that antibodies that bind to and block the processing of pro-HB-EGF not

only inhibit EGFR transactivation but also disrupt the down-stream signaling events and their concomitant effect on predisposition to cancer cell phenotype.

Response to Arguments

The Declarant has not shown that blocking processing *of pro-HB-EGF into HB-EGF* with the polyclonal antibody would also result in affecting proliferation, migration, invasivity and anti-apoptosis in the following specific cancers: colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer. Applicants have made a misstatement on the record that the Declaration in fact shows something that has never been demonstrated in the hands of the inventors. This begs the question, where in the record proceeding have Applicants shown a single working example of an antibody meeting the following characteristics:

a) binds pro-HB-EGF;

b) inhibits activation of any growth-factor receptor of the EGFR family much less HER-2, HER-3 or HER-4;

c) is therapeutically effective *in vivo* against at least one cancer including at least one of colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, and

d) blocks the following cancer activity: proliferation, cell migration, invasivity or anti-apoptosis?

Applicants have yet to satisfy the written description requirement by technical means or under the legal requirements and as recently set forth in the *Ariad* decision See *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc) stating:

"a few broad principles hold across all cases"; "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Conversely, we have repeatedly stated that actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008), or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)."

"For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.

The rejection is maintained.

Enablement

8. The rejection of Claims 2, 8, 10 and 13-17 (and new Claim 18) under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

The rejection was set forth in the Office Action of 7/16/08 as follows:

"Nature of the Invention/ Skill in the Art

Claims 13-16 and (dependent claims 2, 8 and 10) are interpreted as being drawn to a method for the prevention or treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in any cancer, where the cancer is associated with increased G-protein mediated signal transduction and is colon, kidney, bladder, prostatic, breast, lung, or ovarian cancer and where the subject is administered a composition comprising an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF (Claim 13), where the antibody inhibits activation of a GFR of the EGFR family (Claim 14), and the GFR is HER-2, HER-3 or HER-4 (claim 15), where the method is for the treatment (Claim 16), where the GFR is EGFR (Claim 2), where the composition is a pharmaceutical composition comprising the antibody (Claim 8) and the cancer is a human cancer (Claim 10).

Claim 17 is interpreted as being drawn to a method for the treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in any cancer, where the cancer is associated with increased G-protein mediated signal transduction and is colon, kidney, bladder, prostatic, breast, lung, or ovarian cancer and where the subject is

administered a composition comprising an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF.

The relative skill in the art is a clinical oncologist.

Disclosure in the Specification

The specification contemplates using an antibody capable of binding to pro-HB-EGF and which inhibits processing of precursor as an embodiment for affecting a growth-factor receptor ligand precursor. The specification contemplates using the antibody in order to treat *or* prevent a disorder associated with G-mediated signal transduction effecting EGFR where the agent effects a process of cell proliferation, cell migration, invasivity and/or anti-apoptosis. No where in the specification are any methods using an in vitro cell-based assay much less an animal model correlate for any disorder encompassed by the claims showing that the antibody could be practiced in the claimed method and that a prophylactic or therapeutic effect would be accomplished. One of skill in the art could not practice the invention because Applicants have not identified an example of an antibody having the instant claimed properties much less where the antibody is administered to any subject having any cancer. Applicants' prophetic antibody has the alleged properties of preventing just any cancer and treating just any cancer where the general field of art recognizes the unpredictability of preventing/treating just any cancer much less using an immunotherapeutic/ immunoprophylactic antibody in a human subject.

Prior Art Status: Cancer Treatment and Prevention is Unpredictable

A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and drug access to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs. Therefore, the antibody effect(s) in any cancer subject much less a human in the absence of any in vitro cell-based testing or in vivo animal cancer model correlates as in the present case, is not reliable or predictable and further evaluation in cell assays systems and animal tumor systems is essential.

Further, it is not clear what the best approaches are to examining a drug or antibody effect in preclinical testing. Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003); cited in the PTO 892 form of 1/9/08) conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006); cited in the PTO 892 form of 1/9/08) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespedes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs" (p. 325, Col. 1, ¶2).

One skilled in the art would reasonably conclude that evidence obtained in in vitro cell-based assays or even mouse cancer models using the prophetic antibody of applicants invention would not even necessarily correlate with results expected in any human tumor.

Skill in the Art/Undue Experimentation

It appears that undue and inordinate experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of the method for any tumor therapy and any tumor prevention much less in any human. Due the unpredictability of cancer therapeutics in general, as evidenced by Voskoglou-Nomikos, Dennis and Cespedes, *and* in view of the absence of guidance for procuring or making an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF and the absence of working examples concerning the use the prophetic antibody in the method invention, one skilled in the art would not know how to practice the broadly claimed invention. One skilled in the art could not administer to any subject having any cancer "an antibody which binds pro-HB-EGF and which blocks the processing of said pro-HG-EGF" for the treatment and/or prevention of any cancer much less a human cancer and its accompanying pathologies, without undue experimentation."

The rejection was maintained in the Office Action of 3/3/09 as follows:

"Applicants allegations on pp. 7-9 of the Response of 11/17/08 the attached reference article (Molina et al. (Cancer Research, 61:4744-4749 (2001)) and the HERCEPTIN® product data sheet have been carefully considered and are not found persuasive.

A) Applicants have argued that under In re Marzocchi, In re Brana, and In re Bundy that they are not required to produce working examples showing the use of the antibody to treat a cancer and that the Office has not met the burden in showing lack of enablement.

Response to Arguments

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001). Absent a showing to the contrary, arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03).

Applicants have not addressed how to practice using much less the existence of an antibody meeting all of the claim limitations for an antibody that i) binds pro-HB-EGF; ii) blocks the processing of pro-HB-EGF, iii) directly or indirectly effects G-protein mediated signal transduction in a colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, iv) directly or indirectly affects cell proliferation, cell migration, invasivity or anti-apoptosis in a cancer, and v) inhibits activation of a growth-factor receptor of the EGFR family such as HER-2 or EGFR where the method endpoint is treatment of cancer.

Applicants have not addressed how the treatment of any recited cancer with the antibody therapy is enabled when the references of record (Voskoglou-Nomikos; Dennis and Cespedes) teach the unpredictablity of drug therapy much less the complexity in choosing animal model correlates to human diseases. Applicants have not addressed how these references are irrelevant to practicing the method invention in any subject as instantly encompassed by the claims, because Applicants have ignored the general teaching of unpredictability for this art.

Applicants have not addressed how the inventive antibody is better or improved in its ability to access a heterogeneous population of tumor cells in vivo, to internalize within the tumor cell and to block the processing of the pro-HB-EGF protein into a mature HB-EGF protein in order to affect a direct or indirect therapeutic response.

B) Applicants allege "Molina (Cancer Research, 2001) describes the ability of a therapeutically effective antibody Trastuzumab, which binds selectively with high affinity to the extracellular domain of Her2, to inhibit the cleavage of the extracellular domain of the receptor tyrosine kinase Her2 in vitro. The therapeutic antibody has now been utilized for the treatment of tumor patients. See, the disclosure contained Table 1 and Table 2 of the enclosed product brochure on Trastuzumab."

Response to Arguments

The reference article and product data sheet demonstrate a single example of an art recognized antibody, Trastuzumab, that explicitly or inherently meets the limitations in the method for Claims 14 and 15 where the antibody inhibits activation of a growth factor receptor of the EGFR family and the growth factor receptor is HER-2. Molina teaches Trastuzumab was able to effectively block basal and induced HER2 cleavage, and this property was not shared by 2CA, another antibody against the HER2 ectodomain; Trastuzumab is effective in the therapy of breast tumors that overexpressing HER2. The Genetech Trastuzumab product datasheet teaches clinical trial indication for breast cancer and metastatic breast cancer in human patients. Notably, Applicants specification does not even contemplate or provide literal support for Trastuzumab much less any other art recognized antibodies targeting HER-2.

However, the instant method claims also require that *the very same antibody*, and in this example, Trastuzumab, would also have the property of i) binds pro-HB-EGF; ii) blocks the processing of pro-HB-EGF, iii) directly or indirectly effects G-protein mediated signal transduction in a colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer, iv) directly or indirectly affects cell proliferation, cell migration, invasivity or anti-apoptosis in a cancer, and v) achieves the therapeutic endpoint of the method. Applicants have not shown that the Trastuzumab would also block the processing of pro-HB-EGF. The examiner does not believe that pro-HB-EGF (heparin binding-EGF-like growth factor) and HER-2 (C-cerb-2 or Tyrosine kinase-type cell surface receptor HER2) is the same protein molecule, and therefore, it is not understood how the Trastuzumab antibody could affect the two different protein substrates as implied by Applicants. The specification and the cited art does not enable the use of Trastuzumab to bind pro-HB-EGF or block the processing of pro-HB-EGF absent a showing to the contrary.

Claims 14 and 15 would be considered enabled for the aspect of treating breast cancer in vivo using Trastuzumab but the generic Claims 13 and 17 require the same antibody to meet numerous other functional criteria that do not appear to be properties of the Trastuzumab.

The scope of the claims with respect to the kinds of antibodies and the lack of evidence showing the genus of antibodies meeting these requirements does not enable the full scope of the method as discussed above. MPEP 2164.04 states in part: "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work."

The rejection was maintained in the Office Action of 11/6/09 as follows:

"Applicants allegations on pp. 6-7 of the Response of 9/3/09 have been considered and are not found persuasive.

A) Applicants allege the experimental data presented in the 1.132 Declaration of Dr. Ulrich demonstrate that the antibodies of the present invention inhibit EGFR phosphorylation in both control population of cancer cells (i.e., unstimulated cells) as well as cells that have been treated with GPCR agonists LPA and Thrombin. As is shown in Fig. 1 of the enclosed declaration, kidney fibroblast tumor cells (COS-7 cells) treated with GPCR agonists LPA and Thrombin had increased tyrosine phosphorylation of EGFR (as measured via an ELISA assay). However, when the same EGFR transactivated cells were treated with anti-HB-EGF antibodies or the diphtheria toxin mutant CRM 197, a complete reversal of EGFR transactivation was observed. For example, treatment with 20 μg/ml polyclonal anti-HB-EGF antibody completely inhibited LPA-induced and Thrombin induced activation of EGFR to basal levels.

Response to Arguments

Initially the examiner submits that immunotherapeutics was not well-described in the medical literature for just ant antibody much less routine for clinicians and medical professionals in the field of cancer biology and much less even so as here in the present case, where Applicants have yet to describe an animal model correlate for the claimed cancers having been treated in vivo with the claimed antibody.

Four (4) art references spanning nearly 20 years in the field of immuno-therapeutics and as recognizing the complexity of antibody delivery to tumors in vivo are Fujimori et al. (J. Nuc. Med. 31:1191-1198 (1990)); Beckman et al. (Can. 109:170-179 (2007)); Thurber et al. (Adv. Drug Deliv. Rev. 60:1421-1434 (2008)); and Rudnick et al. (Can. Biotherp. & Radiopharm. 24: 155-162 (2009)).

Fujimori teaches for further understanding of Mab distribution in the tumor, one must consider as well the microscopic pharmacology: transport across the capillary wall, transport in tumor interstitium, cellular binding and metabolism. Fujimori discusses predictive models for accessing tumor antigen availability by Mab to examine the relationship between affinity and distribution. Fujimori teaches on p. 1196, Col. 2, ¶1:

> "One strategy to overcome the binding-site barrier would be to increase the initial Mab dose. Even though Mab concentration in tumor does not always increase linearly as initial Mab concentration increases, a high initial plasma concentration leads to better percolation and results in more

uniform distribution in tumor. Increasing Mab dose, however, decreases the specificity ratio and may cause toxicity or other side effects. For each Mab species and set of circumstances, there is an inherent balance of factors. Other causes of heterogeneous distribution include the functional and anatomical heterogeneity of tumors and their vessels..., and the elevated interstitial tissues…"

Beckman teaches on p. 175, Col. 2, ¶2-4:

"Optimizing biodistribution properties of Ab constructs depends on a large number of host and tumor variables. These include: the density and distribution of target Ag in tumors and normal tissues: the degree of target occupancy and residence tiemr equired for tumor cell kill; possible toxicities from normal tissue distribution; tumor size and vascularity; tumor interstitial pressure, convection and diffusion; and metabolism and internilzation rates for Ab-Ag constructs.

An equally large number of Ab construct and therapy variables are available for optimization, including size, charge, and valence; constant region type and glycosylation pattern; presence or absence of a radioisotope or a toxic moiety; dose, route, and schedule of administration; and use of a traditional or a pretargeting strategy. Given the complexity of the problem, systematic preclinical programs may enhance the likelihood of success in subsequent clinical studies. Such preclinical investigations should integrate both experimental and theoretical approaches.

Preclinical studies of a putative Ab-based therapeutic agent can encompass a variety of constructs, differing in molecular weight, affinity, valence, and/or other features of interest, which bind to the same epitope as demonstrated by competition experiments. The Ag density and target affinities should be known for both tumor cells and cross-reacting normal tissues, and the percent target occupancy and required residence time for tumor cell kill should ideally be investigated in vitro. Similarly, rate constants for Ab-Ag internalization should be determined, if applicable. Dose and schedule should be varied and antitumor efficacy, pharmacokinetics, overall biodistribution, homogeneity of intratumoral distribution, and tumor microvessel density and distribution ideally should be measured in tumor-bearing animals with a variety of tumor sizes."

Studies in tumor-bearing rodents are often confounded by lack of normal tissue reactivity with Ab constructs directed toward human Ags, but studies in transgenic animal can be performed in some instances to alleviate this issue."

Thurber teaches on p. 1431, Col 2, ¶3:

"Analyzing the fundamental rates that determine antibody uptake and distribution provides a theoretical framework for understanding and interpreting targeting experiments and improving on the limitations of uptake. It also provides a background for a more rational design of in vitro experiments, animal studies, and clinical trials. The insight gained from this type of modeling has multiple implications for imaging and therapy. For example, not all cells are exposed to the "average" concentration obtained in a tumor. A significant portion of cells can survive even if the tumor-averaged concentration is well above the LD50 in vitro. Also, the concentration that cells in a solid tumor are exposed to ([Ab]surf) is well below the plasma concentration. This means that the bulk antibody concentration in an in vitro spheroid experiment is not analogous to the plasma concentration but is actually well below it; large doses are required to overcome this poor extravasation. Knowing the rate of uptake in a tumor and clearance from the plasma and normal tissues also provides estimates of ratios between tumor and normal tissue concentrations, and these ratios are important in both imaging and therapy. These examples illustrate the utility of combining theoretical analysis also suggest ways to rationally improve uptake, and determining the limiting rates is the first step in overcoming these problems."

Rudnick teaches on p. 155, Col. 2:

"Not strictly limited to tumor cells, target antigen is commonly expressed on normal tissue, found in circulation, and shed into the tumor interstitial space. These nontarget pools of antigens can reduce treatment effectiveness, increase systemic clearance, and increase side-effects (especially for radioimmunoconjugates) by impairing mAb specificity for the tumor."

and on p. 158, Col. 2, last ¶ - p. 159, Col. 1:

"…antigen selection will be a critical factor for internalization and catabolism of mAbs. The relative rates of antigen recycling and dissociation are important in mAb penetration into tumors. Therefore, in applications dependent on targeting every cell of a tumor, the mAb needs to dissociate before it is internalized and degraded. In the case of ADCC, a slow internalizing antigen would be the best target. However, if one is trying to deliver a cytotoxic agent to the cytoplasm of cells in a limited region of a tumor, such as the vasculature, a mAb with slow dissociation targeting a rapidly

recycling antigen would be appropriate. These are just simple examples of the interplay of affinity, avidity, and efficacy in tumor targeting."

Secondly, the Declaration under 37 CFR 1.132 filed 9/3/09 is insufficient to overcome the rejection as set forth in the last Office action because:

The Declarant has not shown the correlation between GPCR-induced phosphorylation of EGFR and HB-EGF, *and* cancer-associated proliferation, migration, invasivity and anti-apoptosis.

The Declarant has not established the relationship or correlation between inhibiting LAP or thrombin (GPCR)-induced EGFR phosphorylation in vitro in immortalized kidney cells (COS-7) by blocking conversion of pro-HB-EGF to HB-EGF with the antibody, and the same polyclonal antibody in treating any cancer cell for proliferation, migration, invasivity and anti-apoptosis in vitro.

The Declarant has not shown that blocking phosphorylation of the EGFR substrate (viz. blocking processing of pro-HB-EGF into HB-EGF with the polyclonal antibody) would also result in affecting proliferation, migration, invasivity and anti-apoptosis in the following specific cancers: colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer or ovarian cancer.

The Declarant has not shown the correlation between inhibiting phosphorylation of the EGFR substrate and the general effect of inhibiting any GPCR-mediated activation of the EGFR family of proteins including HER-2, HER-3 and HER-4.

Finally, the declaration evidence describes the antibodies are against "HB-EGF" and not "pro-HB-EGF" as instantly claimed. Thus the relationship between the antibodies in the declaration data is seemingly unclear to the claimed antibodies. The declaration does not establish a relationship between the different antibodies and their functional properties required to meet the requirements of the claims.

The data in the Declaration are not further enabling for the treatment effect of the polyclonal anti-pro-HB-EGF antibody occurring on proliferation, migration, invasivity and anti-apoptosis for the claimed cancers whether in vitro or in vivo, and the overall inhibitory effect of the antibody on any GPCR-mediated activation of any family member of EGFR including HER-2, HER-3 and HER-4.

B) Applicants allege the disclosure contained in Figures 3-7 and the summary provided in Table 1 of the originally-filed specification shows usefulness of antibody molecules of the instant invention in ameliorating cell proliferation, cell migration, invasivity or anti-apoptosis in the claimed cancers. Applicants cite *In re Irons* for the legal standard for evidentiary proof under a utility rejection.

Response to Arguments

The examiner submits that the data presented in Figures 3-7 for the instant application are wholly irrelevant to the instant claimed method requiring using an anti-pro-HB-EGF antibody. The test compounds, BB94 and AG1478, are not antibodies but small molecule inhibitors. For example, BB94 (batimastat) is a matrix metalloproteinase inhibitor (see attached Tocris datasheet) and AG1478 is an EGFR inhibitor (see attached Tocris datasheet). Applicants have not established the structure/function relationship between the small molecule inhibitors and those antibodies of the instant claims.

As regards Applicants' citation of *In re Irons*, the examiner respectfully submits that the Court's decision does not opine on the enablement requirements for an invention but the asserted utility. The examiner has not questioned the utility of the method or the antibodies nor raised a rejection under 35 U.S.C. 101 to invoke a discussion of *In re Irons*. The decision is silent with respect to enablement.

Applicants allegations on pp. 9-13 of the Response of 5/6/10 have been considered and are not found persuasive.

a) Applicants allege wrt point e) that "It would be reasonable to assume that an antibody which binds to HB-EGF (as shown by the declaration) would also bind to its precursor molecule, pro-HB-EGF.

Response to Arguments

The examiner has established on the record the art-recognized unpredictability for immunotherapeutics and the amount of experimentation required to establish enablement for in vivo therapeutic use of an antibody. Now Applicants are urging the Office to believe that based on hypothetical reasoning for a hypothetical antibody falling within the world of an unpredictable art, the ordinary artisan would be enabled to practice the invention. Absent a showing to the contrary, arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03).

b) Applicants allege wrt point c) that specification exemplifies compounds BB94 and AG1478 that inhibit the initiating EGFR phosphorylation and transactivation events, and prevent the phenotypic changes associated therewith; the totality of Applicants' disclosure demonstrates a correlation between EGFR transactivation and tumorigenesis and compounds which block processing of pro-HB- EGF inhibit the down-stream signaling events and the cancer phenotypes resulting therefrom; and finally, the experiments with COS-7 cells (kidney cancer cells from Cercopithecus aethiops, i.e., grivet) unequivocally demonstrate that the antibodies of the instant invention are, at a minimum, effective against kidney cancer.

Response to Arguments

The examiner has established in the previous Office Action that the small molecule drugs BB94 and AG1478 are non-analogous art (see *Ex parte Murphy v. Burford*) yet Applicants insist on revisiting this aspect of the specification in asserting that claims for an hypothetical antibody are just as enabled as small molecule drugs. Applicants' arguments are irrelevant to the extent that they have not shown the

structure/function correlation between the small molecule drugs and the hypothetical antibody. The examiner and the Office do not have the technical resources for performing the algorithm(s) and/or necessary experimentation in making any such comparative assessment.

The examiner concurs that in the Declaration, proliferation for the kidney cancer cell line COS-7 was inhibited *in vitro* by the polyclonal antibody against HB-EGF. However, where in the prosecution proceeding has there been a demonstration of an in vivo model using the COS-7 cell line and the anti-pro-HB-EGF antibody? Finally, where in the instant case, the Examiner has established on the record the unpredictability of translating in vitro therapeutics to similar or comparable in vivo therapeutic results, Applicants have not even shown that in vitro results for the COS-7 cell line is recognized as correlating to a specific condition (animal kidney cancer model much less for human kidney cancer (MPEP 2164.02)).

c) Applicants allege wrt point b) that the evidence of record shows the pathway relationship for LPA or thrombin- induced in vitro EGFR phosphorylation in cancer cells and the utility of the claimed inhibitory compounds in reversing the cancer cell phenotype resulting from EGFR transactivation (i.e., proliferation, migration, invasivitiy, and anti-apoptosis).

Response to Arguments

The examiner agrees that the evidence of record shows this relationship for the intra-cellular pathway.

d) Applicants allege wrt to point a) the data in the declaration clearly demonstrates that antibodies against HB-EGF are suitable for treating hyperproliferative diseases, i.e., diseases associated with ceil proliferation, and in particular diseases that are associated with an abnormal GPCR-induced receptor tyrosine kinase signal; anti-HB-EGF-induced inhibition of cancer ceil phenotypes is further described in the co-owned post-published European patent application EP 08 802 677.8 (published as WO 09/040134).

Response to Arguments

For all the reasons set forth above and for purposes of brevity, Applicants have not established on the record a working example of an anti-pro-HG-EGF antibody having the cancer therapeutic effect in vivo for any cancer much less the kidney cancer where the COS-7 tumor cell line is used as the art-recognized animal model correlate for mammalian kidney cancer.

e) Applicants allege they are not required to show in vivo clinical data.

Response to Arguments

Applicants are requested to identify by exact page, paragraph and line where in the record proceeding they have been required to submit clinical trial data. Applicants are not required to show human clinical data. MPEP 2164.05 states in part:

> "Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention. In chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted."

However, the issue is whether the in vitro COS-7 cell line assays described in the specification can be reasonably correlated to in vivo animal studies using the same

kidney cancer cells and any antibody that binds pro-HB-EGF. MPEP 2164.02 states in part:

> "The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications)."

The examiner's search of PubMed literature database for the use of COS-7 kidney cells in an animal model for kidney cancer and where any therapeutic antibody was tested for in vivo therapeutic effect did not identify any hits. Applicants are invited to supplement the record with examples of literature references showing the art-recognized correlation for the COS-7 cell line in vitro with the in vivo correlation to animal kidney cancer.

f) Applicants allege under *In re Marzocchi* working examples are not required to establish enablement and the method can be practiced without undue experimentation.

Response to Arguments

The examiner resubmits that in a hypothetical world as for the present case, that the ordinary artisan could certainly understand from reading the specification the steps

for making and testing an antibody against pro-HB-EGF, testing the antibody on cancer cells in vitro and in vivo, and then determining whether the therapeutic effects were mediated by blocking proliferation, cell migration, invasivity or producing anti-apoptosis. In the real world, the ordinary artisan would be required to screen several different antibodies meeting all of the functional requirements for the instant claims. If the method was intended to be practiced in a human, then a reasonable number of carefully performed models would need to be performed and that were art-recognized at the time of filing as having a disease correlation with kidney cancer unless there is/are cell line-based assays that permit extrapolation of the results to in vivo therapeutics.

Applicants are left with the question how the ordinary artisan could possibly achieve all of this in the absence of undue experimentation. Applicants themselves seem to be in a similar position because they have relied on attorney arguments and reference articles relating to unrelated antibodies in alleging they would perform the same function as the hypothetical anti-pro-HB=EGF antibody in vivo. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)).

The rejection is maintained.

Conclusion

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner
Art Unit 1643